1,2-BENZISOXAZOL-3-YL COMPOUNDS

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(52) U.S. Cl. 514/321; 546/198

(58) Field of Classification Search 514/321; 546/198

See application file for complete search history.

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ABSTRACT

This invention relates to novel 1,2-benzisoxazol-3-yl compounds,
their derivatives, pharmaceutically acceptable salts, solvates,
and hydrates thereof. This invention also provides compositions
comprising a compound of this invention and the use of such compositions
in methods of treating diseases and conditions that are beneficially treated by administering
an antagonist of both dopamine and serotonin receptors.

9 Claims, No Drawings
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1 1,2-BENZISOXAZOL-3-YL COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. §119 to U.S. Provisional Application Ser. No. 60/911,669, filed Apr. 13, 2007, the entire contents of which are incorporated by reference herein.

This invention relates to novel 1,2-benzisoxazol-3-yl compounds, their derivatives, pharmaceutically acceptable salts, solvates, and hydrates. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administrating an antagonist of both dopamine and serotonin receptors.

Iloperidone is an antipsychotic, serotonin/dopamine receptor antagonist. Iloperidone is also known as Fiapta® and Zomaril®, and by the chemical names 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyphenyl]ethanone; 1-[3-(4-acetyl-2-methoxyphenoxy)propyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine; and 4-[3-(4-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyacetophenone. It is pre-registered with the FDA for the treatment of schizophrenia following a phase III clinical trial and is currently being tested for safety and efficacy in patients with an acute exacerbation of the disease. It is also in phase I clinical trials for bipolar disorder.

The reduced metabolite of iloperidone, known by the chemical names 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxy-c-methylbenzene methanol and 1-[(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)propoxy]-3-methoxypheny]ethanol, also has serotonin/dopamine receptor antagonist activity. See, Mutlib A E et al., J Pharmacol Exp Ther 1998, 286:1285 and PCT publication WO 03/020707.

Iloperidone demonstrated variable clinical effect resulting from the level of CYP2D6 activity in patients receiving the drug. This is of concern because iloperidone is known to prolong a subject’s QTc interval. For example, in patients with low CYP2D6 activity, a given dose of iloperidone can result in much higher exposure than intended and thus result in QTc prolongation. See WO 06/039663. Prolonged QTc intervals are associated with an increased risk of developing ventricular arrhythmias and can result in sudden death. In a phase III clinical trial for iloperidone, it was found that the QTc prolongation in good metabolizers of iloperidone was shorter (10.4 msec) than in poor metabolizers (15.0 msec). See Vanda Pharmaceuticals Press Release, Dec. 7, 2006.

Common side effects of iloperidone include nausea, anxiety, dizziness, insomnia, low blood pressure, muscle stiffness, muscle pain, sedation, tremors, increased salivation, and weight gain (e.g., gains of greater than 50 pounds). These compounds have also been known to cause sexual dysfunction (e.g., retrograde ejaculation). Additionally, breast tenderness and lactation (in both genders) may occur. Many antipsychotics are known to increase prolactin because they inhibit dopamine. Thus, iloperidone can potentially cause tardive dyskinesia (TD), extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome (NMS).

Despite the beneficial activities of iloperidone, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

DEFINITIONS

The terms “ameliorate” and “treat” are used interchangeably and include therapeutic and/or prophylactic treatment.
with a reasonable benefit/risk ratio. A “pharmacologically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A “pharmacologically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartric acid, ascorbic acid, maleic acid, benzoic acid, fumaric acid, gluconic acid, gluconic acid, fumaric acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carboxylic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzate, chlorobenzozate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

As used herein, the term “hydrate” means a compound which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein, the term “solvate” means a compound which further includes a stoichiometric or non-stoichiometric amount of solvent such as, e.g., water, acetone, ethanol, methanol, dichloromethane, 2-propanol, or the like, bound by non-covalent intermolecular forces.

The compounds of the present invention (e.g., compounds of Formula I), may contain one or more more stereogenic centers. Accordingly, compounds of this invention can exist as either individual stereoisomers or mixtures of two or more stereoisomers. A compound of the present invention will include both mixtures (e.g., racemic mixtures) and also individual respective stereoisomers that are substantially free from another possible stereoisomer. The term “substantially free of other stereoisomers” as used herein means less than 25% of other stereoisomers, less than 10% of other stereoisomers, or less than “X%” of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are taken together, with the carbon atom to which they are bound, to form a carbonyl group; or

wherein:

R1ab and R1bc are each independently selected from —CH3, —CH2D, -CHD2, and -CD3;

R2 is —CH2D2n CHnD2m CH2D2p; wherein each of n, m, and p is independently selected from 0, 1, and 2 (R2 may also be referred to as an n-propylene wherein 1 to 6 hydrogen atoms are optionally replaced by deuterium);

R3a is selected from H, D, and F;

R3b is selected from H, D, and F; and, when R3b is H or D, R3b is additionally selected from —OH; or

R3a and R3b are taken together, with the carbon atom to which they are bound, to form a carbonyl group; or

R3a and R3b are taken together, with the carbon atom to which they are bound, to form a cyclopropyl ring; and

at least one R group (i.e., R1a, R1b, R2, R3a, and R3b) comprises a deuterium atom.

The present invention provides an isolated compound of Formula I, which includes salts, hydrates, and solvates thereof,
wherein:

- R^1a and R^1b are each independently selected from —CH_3, —CH_2D, CHD, and CH_2D;
- R^2 is —CH_2D, —CHD, or each of R^1a, R^1b, and R^2 is additionally selected from —CD_3 and —CD_2CH_2;
- R^3a and R^3b are each independently selected from 0 and 2. In other words, R^2 and R^3 are taken together, with the carbon atom to which they are bound, to form a carbonyl group; or
- wherein:
  - R^3b is selected from H, D, and F, and, when R^3b is selected from H, D, and F; or
  - R^3b is additionally selected from —OH; or
  - R^3b and R^3 are taken together, with the carbon atom to which they are bound, to form a carbonyl group; or
  - in another embodiment, R^3a and R^3b are taken together, with the carbon atom to which they are bound, to form a cyclopropyl ring; and
  - at least one R group (i.e., R^1a, R^1b, R^2, R^3a, and R^3b) comprises a deuterium atom.

For the avoidance of doubt, the orientation of R^2 in a compound of Formula I is such that the CH_3D_2-methylene unit (or the left-most indicated methylene unit) is bound to the piperaldinyl nitrogen.

In one embodiment, each of R^1a and R^1b is independently selected from CH_3 and CD_3.

In another embodiment, R^1a and R^1b are simultaneously CD_3.

In still another embodiment, R^1a is CD_3 and R^1b is CH_3.

In yet another embodiment, each of R^1a, R^1b, and R^p is independently selected from 0 and 2. In other words, R^2 is selected from CH_3CH_2CH_2, CH_3CHDCH_2, CH_3CD_2CH_2, CH_3CD_2CD_2, CD_3CD_2CH_2, CD_3CD_2CD_2, CD_2CD_2CH_2, and CD_2CD_2CD_2.

In certain embodiments, m is 2. In other words, R^2 is selected from CH_3CH_2CH_2, CH_3CHDCH_2, and CH_3CD_2CH_2.

In other embodiments, m is 0 and each of n and p is independently selected from 0 and 2. In other words, R^2 is selected from CH_3CD_2CD_2, CH_3CD_2CH_2, CD_3CD_2CD_2, CD_3CD_2CD_2, CD_2CD_2CH_2, and CD_2CD_2CD_2.

In still other embodiments, R^3a is hydrogen and R^3b is selected from —OH and F.

In another embodiment, R^3a and R^3b are taken together, with the carbon atom to which they are bound, to form a carbonyl group.

In still other embodiments, R^3a and R^3b are simultaneously D.

In still other embodiments, R^3a and R^3b are simultaneously F.

In another embodiment, the compound is any one of the compounds set forth in Table 1:

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In a more specific embodiment, the compound of Formula I is selected from:

![Compound 131]
In another specific set of embodiments, each atom not specified as deuterium in any of the compounds of the foregoing embodiments is present at its natural isotopic abundance.

In another set of embodiments, the compound of Formula I is isolated or purified, e.g., the compound of Formula I is present at a purity of at least 50% by weight (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, 99.5% or 99.9%) of the total amount of isotopologues of Formula I present. Thus, in some embodiments, a composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 50% of the isotopologues by weight are the recited compound.

In some embodiments, any position in the compound of Formula I designated as having D has a minimum deuterium incorporation of at least 45% (e.g., at least 52.5%, at least 60%, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5%) at the designated position(s) of the compound of Formula I.

Thus, in some embodiments, a composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 45% of the isotopologues include a D at the designated position(s).

In some embodiments, a compound of Formula I is “substantially free of” other isotopologues of the compound, e.g., less than 50%, less than 25%, less than 10%, less than 5%, less than 2%, less than 1%, or less than 0.5% of other isotopologues are present.

Exemplary Syntheses


Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds defined herein or by invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

One generally applicable synthesis for preparing compounds of Formula I involves coupling together two starting materials via a substitution reaction, as depicted in Scheme 1.

Scheme 1: Exemplary Synthesis of Compounds of Formula I
Scheme 1 illustrates that the compounds of Formula I can be readily prepared by a substitution reaction in which a piperidinyl compound (5) displaces a chloride leaving group on an appropriately deuterated 4-(3-chloropropoxy)-3-methoxyphenyl intermediate (6). The groups $R^{1a}$, $R^{1b}$, $R^{3a}$, and $R^{3b}$ are as defined above in Formula I. The optionally-deuterated bridging propyl group ($R^2$) in Formula I is represented structurally in Scheme 1, and each $Z$ is independently hydrogen or deuterium. In one synthetic strategy, intermediate (6) comprises the sites of optional deuteration that may ultimately be incorporated into the compounds of Formula I.

Scheme 2 illustrates exemplary syntheses of a deuterated intermediate, such as intermediate (14) or intermediate (17), either of which may subsequently be utilized in place of intermediate (6) in Scheme 1, to provide compounds of Formula I.

Scheme 2: Synthetic Routes to Intermediates 14 and 17

Alternatively, (13) can be alkylated with methyl 3-bromopropionate under analogous conditions to provide (15). The alcohol group in (16) can be converted to a chloride by the methods described by Yoshihara, M et al, Synthesis 1980, 9: 746, followed by deprotection of the secondary alcohol to provide (17). Like (14), intermediate (17) can undergo a substitution reaction with Compound 5, as shown in Scheme 1, in order to provide a compound of Formula I.

Scheme 3: Alternate Approach to the Synthesis of Compounds of the Structure of Intermediate 6

Starting material (12), which may be prepared as described by Markey S P et al, J Label Comp Radiopharm 1980, 17:103, can be reacted with the Grignard reagent derived from iodomethane (i.e., $R^{1b}$-CH$_3$) or iodomethane-d$_3$ (i.e., $R^{1b}$-CD$_3$) to provide (13). See Sharma A et al, Bull Chem Soc Jap 2004, 77: 2231. As illustrated, this reaction provides a mixture of enantiomers. If desired, this mixture can be resolved to afford stereoisomerically pure (13) or, alternatively, any subsequent product derived from (13) may be resolved using techniques well known in the chemical arts. Compound (13) can then be alkylated with 3-chloropropyl bromide, under basic conditions (e.g., potassium carbonate in DMF), to yield (14). See Strupczewski, J T et al, J Med Chem 1995, 38: 1119. Intermediate (14) can then be used in place of (6) in the substitution reaction illustrated in Scheme 1.
Compositions

The invention also provides pyrogen-free compositions comprising an effective amount of a compound of Formula I or a pharmaceutically acceptable salt, solvate, or hydrate thereof, and an acceptable carrier. In one embodiment, a composition of this invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in amounts typically used in medicaments.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, gum tragacanth, gum acacia, the water-soluble polyalcohols, such as mannitol, sorbitol, xylitol, malic acid, emulsifying salts, such as sodium lauryl sulfate, calcium stearate, sorbitan laurate, and the like. Proteins and albumins may be used as adjuvants. Buffers, such as acetate, citrate, lactate, tartrate, phosphate, and other buffers, may be added to the compositions to maintain the pH of the preparation within a pharmaceutically acceptable range.

Additional diluents, such as lactose, sucrose, microcrystalline cellulose, dicalcium phosphate, silicic acid, talc, and the like, may be included in the compositions. In certain embodiments, a liquid diluent, such as a polyethylene glycol, may be added to the compositions. Pharmaceutical carriers suitable for parenteral administration include saline solutions and D5WO, and other such carriers as are well known in the art.

Additional examples of pharmaceutically acceptable carriers include, but are not limited to, paraffin oil, lanolin, synthetic gyrochrome, synthetic wax, polyethylene glycol and wool fat. Waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol, sorbitol, polyethylene glycol 400, polyethylene glycol 6000 or a pharmaceutically acceptable salt, solvate, or hydrate thereof, and an acceptable carrier.

In one embodiment, a pharmaceutical composition comprises an effective amount of a compound of Formula I and pharmaceutically acceptable carriers, adjuvants and vehicles. In another embodiment, the pharmaceutical composition comprises an effective amount of a compound of Formula I and pharmaceutically acceptable carriers, adjuvants and vehicles. The pharmaceutical compositions of the invention include aqueous and non-aqueous formulations. Suitable non-aqueous formulations, as suspensions, solutions, or emulsions, may be injected intramuscularly, intravenously, subcutaneously, or intradermally. Pharmaceutically acceptable carriers include water, saline, sodium chloride, glycerin, propylene glycol, ethanol and the like. In particular, the compositions may be administered transdermally (e.g., using a transdermal patch or iontophoretic techniques).

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTRÔX™ and PLURONICTM (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Pat. No. 7,014,866; and United States patent publications 20060094744 and 20060079502.

The pharmaceutical compositions of the invention include suitable formulations for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th Ed. (1985).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

For Organic Synthesis,

Fieser's Reagents for Organic Synthesis,

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g., U.S. Pat. No. 6,803,031.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene fatty polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compositions of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polyethyleneoxide, polysaccharide, polyethylene glycol, polyactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.
According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible (e.g., because of removal from the patient or surgical procedure) such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound known to antagonize either or both dopamine and serotonin receptors. Such agents include but are not limited to those known to antagonize either or both dopamine and serotonin receptors. Such agents may include but are not limited to those described as being useful in combination with loperamide, risperidone, paliperidone or agents of the same chemical class, such as disclosed in U.S. Pat. Nos. 5,364,866; 5,776,963, 6,100,256; 6,147,072; 6,150,355; 6,166,008; 6,174,886; 6,229,875; 6,237,336; 6,384,077; 6,689,812; 6,420,369; 6,620,819; 6,444,665; 6,495,154; 6,566,389; 6,680,310; and 6,964,962.

In another embodiment, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from the following diseases and conditions: affective psychosis aggression; Alzheimer disease; Alzheimer type dementia; Alzheimer type senile dementia; amphetamine dependence (e.g., methamphetamine dependence); anorexia nervosa; anxiety disorder; Asperger’s disorder; bipolar disorders (e.g., bipolar I disorder, bipolar mania, and bipolar depression); child development disorders; cocaine dependence; conduct disorder; dementia with agitation; diabetes (e.g., type 2 diabetes mellitus); hyperglycemia; hyperprolactinemia; insulin resistance; major depressive disorders (e.g., major depressive disorder with panic attacks, major depressive disorder with suicidality) mania; metabolic syndromes (e.g., metabolic syndrome X); mood disorders; obsessive-compulsive disorder; panic disorder; post-traumatic stress disorders; prodromal schizophrenia; psychosis; psychotic disorders (e.g., psychotic disorder NOS); schizoaffective disorder; schizophrenia; schizophreniaiform disorder; and substance abuse (e.g., marijuana abuse and alcohol abuse).

In another embodiment, the second therapeutic agent is selected from lithium, valproate, carbamazepine, haloperidol, ADP-103, clozapine, bromocriptine, olanzapine, quetiapine, aripiprazole, cariprazolam SB-773812, risperidone, valnoctamide, licarbazepine, fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran, duloxetine, amino acids and their derivatives, topiramate, acetaminophen, indomethacin, Tylenol #3, melatonin, tricyclic antidepressants, anticonvulsants, serotonin reuptake inhibitors, mixed serotonin-norepinephrine reuptake inhibitors, serotonin receptor agonists and antagonists, cholinoergic analogues, adrenergic agents, neurokinin antagonists, milpristine, cyamemazine, and reboxetine.

In another embodiment, the second therapeutic agent is selected from melatonin, (1R-Trans)-N-[2-(2,3-dihydrobenzofuran-4-yl)pyrrolidin-3-yl]-N-ethylurea, ramelteon, GR196429, LY156735, agomelatine, 2-phenylmelatonin, 8-M-PDOT, 2-iodomelatonin, 6-chloromelatonin, TAK-375, CGP 52608, GR196429, S20242, S-23478, S24268, S25150, GW-290569, and IP-101. In a still more specific embodiment, the second therapeutic agent is selected from melatonin, (1R-Trans)-N-[2-(2,3-dihydrobenzofuran-4-yl)pyrrolidin-3-yl]-N-ethylurea, ramelteon, GR196429, LY156735, agomelatine, 2-phenylmelatonin, 8-M-PDOT, 2-iodomelatonin, and 6-chloromelatonin.

In another embodiment, the compound of Formula I and one or more of any of the above-described second therapeutic agents are provided as separate dosage forms, wherein the compound and second therapeutic agent are associated with one another. The term “associated with one another” as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term “effective amount” refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.


In one embodiment, an effective amount of a compound of this invention can range from about 0.06 μg/kg to about 300 mg/kg.

In another embodiment, an effective amount of a compound of this invention can range from about 0.6 μg/kg to about 30 mg/kg.

In another embodiment, an effective amount of a compound of this invention can range from about 6 μg/kg to about 3 mg/kg.

Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapy dose. The normal monotherapy dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., Eds., Pharmacotherapy Handbook, 2nd Ed., Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Pub...
It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a mono-therapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

In another embodiment, the invention provides a method of modulating the activity of a dopamine and/or a serotonin receptor in a cell, comprising contacting the cell with one or more compounds of Formula I herein. The cell can be a cell of a mammal, e.g., human, monkey, horse, cow, rat, mouse, cat, dog, sheep, or pig.

According to another embodiment, the invention provides a method of treating a subject suffering from, or susceptible to, a disease that is beneficially treated by modulating the activity of dopamine and/or serotonin receptors in a cell, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention.

Such diseases are well known in the art and include, but are not limited to the following diseases and conditions: affective psychosis, schizophrenia, Alzheimer disease, Alzheimer type dementia, Alzheimer type senile dementia, amphetamine dependence (e.g., methamphetamine dependence), anorexia nervosa, anxiety disorder, Asperger’s disorder, bipolar disorders (e.g., bipolar 1 disorder, bipolar mania, and bipolar depression), child development disorders, cocaine dependence, conduct disorder, dementia with agitation, diabetes (e.g., type 2 diabetes mellitus), hyperglycemia, hyperprolactinemia, insulin resistance, major depressive disorders (e.g., major depressive disorder with panic attacks, major depressive disorder with suicidality), mania, metabolic syndromes (e.g., metabolic syndrome X), mood disorders, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorders, prodromal schizophrenia, psychosis, psychotic disorders (e.g., psychotic disorder NOS), schizoaffective disorder, schizophrenia, schizophreniform disorder, and substance abuse (e.g., marijuana abuse and alcohol abuse). In a particular embodiment, the combination therapies of this invention include the treatment of schizophrenia.

In another specific embodiment, the second therapeutic agent is useful in treating a patient suffering from or susceptible to a disease or condition selected from schizophrenia, depression, insomnia and psychosis.

In another specific embodiment, the second therapeutic agent is melatonin or a melatonin agonist. In an even more specific embodiment, the second therapeutic agent is selected from melatonin, (1R-Trans)-N-[2-(2,3-dihydro-4-benzofuran-4-yl)cyclo-propyl]methyl[propanamide, N-[1-(2,3-dihydrobenzofuran-4-yl)pyrrolidin-3-yl]-N-ethylurea], ramelteon, GR196429, LY156735, agomelatine, 2-phenylmelatonin, 8-M-PDOT, 2-iodomelatonin, and 6-chloromelatonin; and the patient is suffering from or susceptible to insomnia or depression.

The term “co-administered” as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods.

The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., Eds., Pharmacotherapy Handbook, 2nd Ed., Appleton and Lange, Stumford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan’s purview to determine the second therapeutic agent’s optimal effective-amount range.

In another embodiment, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages
(including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In another embodiment, this invention provides for the use of a compound of Formula 1, alone or together with one of the above-described second therapeutic agents, in the manufacture of a medicament, either in a single composition or in separate dosage forms, for treating a disease that is beneficially treated by modulating the activity of dopamine and/or serotonin receptors in a cell. Such diseases are well known in the art and are disclosed in clinical trial number NCT00254202 and include affective psychosis aggression, Alzheimer disease, Alzheimer type dementia, Alzheimer type senile dementia, amphetamine dependence (e.g., methamphetamine dependence), anorexia nervosa, anxiety disorder, Asperger's disorder, bipolar disorders (e.g., bipolar I disorder, bipolar manic, and bipolar depression), child development disorders, cocaine dependence, conduct disorder, dementia with agitation, diabetes (e.g., type 2 diabetes mellitus), hyperglycemia, hyperprolactinemia, insulin resistance, major depressive disorders (e.g., major depressive disorder with panic attacks, major depressive disorder with suicidal ideation, mania, metabolic syndromes (e.g., metabolic syndrome X), mood disorders, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorders, prodromal schizophrenia, psychosis, psychotic disorders (e.g., psychotic disorder NOS), schizophrenia, schizophreniform disorder, and substance abuse (e.g., marijuana abuse and alcohol abuse).

Diagnostic Methods and Kits

The compounds and compositions of this invention are also useful as reagents in methods for determining the concentration of iloperidone or the reduced metabolite of iloperidone in a solution or biological sample such as plasma, for examining the metabolism of iloperidone or the reduced metabolite of iloperidone, and for other analytical studies. Additional utility of compounds of Formula 1 include their use as internal standards, or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a “refill” of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In another embodiment, the container is a blister pack.

The kit may additionally comprise a memory aid of the type containing information and/or instructions for the physician, pharmacist or subject. Such memory aids include numbers printed on each chamber or division containing a dosage that corresponds with the days of the regimen which the tablets or capsules so specified should be ingested, or days of the week printed on each chamber or division, or a card which contains the same type of information. For single dose dispensers, memory aids further include a mechanical counter which indicates the number of daily doses that have been dispensed and a battery-powered micro-chip memory coupled with a liquid crystal readout and/or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is

Measuring devices that can distinguish iloperidone or the reduced metabolite of iloperidone from a corresponding compound of Formula 1 include any measuring device that can distinguish between two compounds that differ from one another in isotopic abundance. Exemplary measuring devices include a mass spectrometer, NMR spectrometer, and IR spectrometer.

In another embodiment, the invention provides a method of evaluating the metabolic stability of a compound of Formula 1, comprising the steps of contacting the compound of Formula 1 with a metabolizing enzyme source for a period of time and comparing the amount of the compound of Formula 1 with the metabolic products of the compound of Formula 1 after the period of time.

In a related embodiment, the invention provides a method of evaluating the metabolic stability of a compound of Formula 1 in a subject following administration of the tablets of Formula 1. This method comprises the steps of obtaining a serum, urine, or feces sample from the subject at a period of time following the administration of the compound of Formula 1 to the subject and comparing the amount of the compound of Formula 1 with the metabolic products of the compound of Formula 1 in the serum, urine, or feces sample.

The present invention also provides kits for use to treat any of the diseases or disorders described previously, including, e.g., schizophrenia. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula 1 (including a salt, hydrate, or solvate thereof), wherein the pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat schizophrenia.

The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition.

Examples include bottles, ampules, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a “refill” of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In another embodiment, the container is a blister pack.
to be taken. Other memory aids useful in such kits are a calendar printed on a card, as well as other variations that will be readily apparent.

The kits of this invention may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

EXAMPLES

Example 1

Synthesis of 1-((4-hydroxy-3-methoxy-d3-phenyl)ethanone (Intermediate 26)

Intermediate 26 was prepared as outlined in Scheme 4, below. Details of the synthesis are set forth below.

Scheme 4: Synthesis of Intermediate 26

Synthesis of 2-(4-(benzyloxy)-3-fluorophenyl)-2-methyl-1,3-dioxolane (23)

A mixture of 1-((4-hydroxy-3-fluorophenyl)ethanone (22) (23.8 g, 97.5 mmol), ethylene glycol (164 mL, 293 mmol), p-TsOH (930 mg, 4.88 mmol) and toluene (400 mL) was stirred under reflux conditions for 4 days, azeotropically removing water with a Dean-Stark trap. The mixture was cooled to room temperature and quenched by addition of saturated sodium bicarbonate solution (200 mL). The aqueous phase was back-extracted with toluene (3x200 mL). The combined organic phases were washed with brine (200 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give 28.7 g (103%) of crude 23 as a yellow solid. Crude 23 was used without further purification. 1H NMR (CDCl3) δ: 7.39 (m, 5H), 7.22 (dd, 1H), 7.16 (dd, 1H), 6.95 (t, 1H), 5.12 (s, 2H), 4.12 (dd, 2H), 3.77 (dd, 2H), 1.62 (s, 3H). LCMS m/z=289.1 (M+H).

Synthesis of 2-(4-(benzyloxy)(3-methoxy-d3)phenyl)-2-methyl-1,3-dioxolane (24)

A mixture of potassium t-butoxide (24.8 g, 214.3 mmol), methanol-d3 (11.8 mL, 299 mmol), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (17.6 mL) and toluene (44 mL) was heated at 100°C for 0.5 hour (hr) to give a yellow suspension. Compound 23 (16.3 g, 56.4 mmol) was added and the mixture heated at 100°C overnight. The mixture was cooled to room temperature, washed with water (200 mL) and 6N HCl (100 mL). The aqueous washings were combined and extracted with ethyl acetate (4x150 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to give 18 g of crude 24. Crude 24 was used directly for the next step without further purification. 1H NMR (CDCl3) δ: 7.39 (m, 5H), 7.02 (d, 1H), 6.96 (d, 1H), 6.82 (d, 1H), 5.18 (s, 2H), 4.02 (dd, 2H), 3.78 (dd, 2H), 1.62 (s, 3H). LCMS m/z=304.1 (M+H).

Synthesis of 1-(4-(benzyloxy)-3-fluorophenyl)ethanone (25)

A mixture of crude 24 (18 g, 56.4 mmol) and p-TsOH (86 mg, 2.82 mmol) in acetone (150 mL) and a few milliliters of water was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product that was purified by column chromatography using 0-100% ethyl acetate/hexanes to give 14 g (96%) of 25. 1H NMR (CDCl3) δ: 7.56 (m, 2H), 6.96 (d, 1H), 6.06 (s, 1H), 2.57 (s, 3H). LCMS m/z=260.1 (M+H).

Synthesis of 1-((4-hydroxy)-3-methoxy-d3-phenyl)ethanone (26)

A mixture of 25 (14 g, 56.4 mmol) and 20% Pd—C (700 mg, 5 wt %) in methanol (20 mL) and ethyl acetate (20 mL) was hydrogenated at 4 Bar H2 for 2 hr. The mixture was filtered through a pad of Celite, washing the pad with ethyl acetate (200 mL). The filtrate solution was concentrated under reduced pressure and the crude product purified by column chromatography using 0-100% ethyl acetate/hexanes to give 2 g (22%) of 26. 1H NMR (CDCl3) δ: 7.56 (m, 2H), 6.96 (d, 1H), 6.06 (s, 1H), 2.57 (s, 3H). LCMS m/z=170.1 (M+H).

Example 2

Synthesis of 1-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)propoxy)-3-methoxy-d3-phenyl)ethanone (Compound 131)

The synthesis of compound 131 was carried as outlined in Scheme 5, below. Details of the synthesis are set forth below.
Scheme 5: Synthesis of Compound 131

D<sub>3</sub>CO

HO

BrCI

K<sub>2</sub>CO<sub>3</sub>

acetone

reflux

26

5

D<sub>3</sub>CO

Cl

K<sub>2</sub>CO<sub>3</sub>, DMF, 90° C.

27

10

Synthesis of 1-(4-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-yl)propoxy-d<sub>6</sub>)-(3-methoxy-d<sub>3</sub>)phenyl)ethanone (Compound 141)

A mixture of 26 (1 g, 5.9 mmol) and potassium carbonate (1.6 g, 11.8 mmol) in acetone (20 mL) was refluxed for 1.5 hr, then cooled to room temperature. Acetone was removed by concentration under reduced pressure to the crude potassium salt of 26 as a white powder. The crude salt was added in small portions over 4 hr to a refluxing solution of d<sub>6</sub>-dibromopropane (3.7 g, 17.7 mmol) in acetone (10 mL). After addition of the salt was complete, the reaction mixture was refluxed for 0.5 hr, then cooled to room temperature and stirred overnight. The product was isolated and purified by column chromatography on silica gel using 1:1 heptanes/ethyl acetate to give 1.2 g (68%) of 28 as a white solid. 1H NMR (CDCl<sub>3</sub>) 8: 7.58 (m, 2H), 6.92 (d, 1H), 2.54 (s, 3H). LCMS m/z = 296.0 (M+H).

Synthesis of 1-(4-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-yl)propoxy-d<sub>6</sub>)-(3-methoxy-d<sub>3</sub>)phenyl)ethanone (Compound 131)

A mixture of 28 (0.82 g, 2.76 mmol), 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride (5, 0.71 g, 2.76 mmol) and potassium carbonate (0.77 g, 5.6 mmol) in DMF (10 mL) was heated at 90° C. overnight. After cooling to room temperature, the solid was filtered and washed with DMF (100 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel using 0-10% methanol/dichloromethane to give 650 mg (55%) of Compound 141 as a yellow solid. 1H NMR (CDCl<sub>3</sub>) 8: 7.65 (q, 1H), 7.58 (m, 2H), 7.21 (m, 1H), 7.06 (m, 1H), 6.92 (d, 1H), 4.23 (t, 2H), 3.76 (t, 2H), 2.58 (s, 3H), 2.34 (m, 2H). LCMS m/z = 436.2 (M+H).

Evaluation of Compound Stability

Certain in vitro liver metabolism studies have been described previously in the following references, each of which is incorporated herein in their entirety: Obach R S, Drug Metab. Disp. 1999, 27: 1350; Houston, J B et al., Drug Metab. Rev. 1997, 29: 891; Houston, J B Biochem Pharmacol 1994, 47: 1469; Iwatsubo T et al., Pharmacol. Ther. 1997, 73: 147; and Lave, T et al., Pharm. Res. 1997, 14: 152.

Microsomal Assay: The metabolic stability of compounds of Formula I is tested using pooled liver microsomal incubations. Full scan LC-MS analysis is then performed to detect major metabolites. Samples of the test compounds, exposed to pooled human liver microsomes, are analyzed using UPLC-MS (or MS/MS) detection. For determining metabolic stability, multiple reaction monitoring (MRM) is used to mea-
Incubation of Test Compounds with Liver Microsomes: The reaction mixture, minus cofactors, is prepared. An aliquot of the reaction mixture (without cofactors) is incubated in a shaking water bath at 37°C for 3 minutes. Another aliquot of the reaction mixture is prepared as the negative control. The test compound is added into both the reaction mixture and the negative control at a final concentration of 1 μM. An aliquot of the reaction mixture is prepared as a blank control, by the addition of plain organic solvent (no test compound added). The reaction is initiated by the addition of cofactors (not added to the negative controls), and then incubated in a shaking water bath at 37°C. Aliquots (200 μL) are withdrawn in triplicate at multiple time points (e.g., 0, 15, 30, 60, and 120 minutes) and combined with 800 μL of ice-cold 50/50 acetonitrile/dH2O to terminate the reaction. The positive controls, testosterone and propranolol, as well as iloperidone, are each run simultaneously with the test compounds in separate reactions.

All samples are analyzed using LC-MS (or MS/MS). An LC-MRM-MS/MS method is used to examine metabolic stability. Also, Q1 full scan LC-MS methods are performed on the blank matrix and the test compound incubation samples. The Q1 scans serve as survey scans to identify any sample unique peaks that might represent the possible metabolites. The masses of these potential metabolites can be determined from the Q1 scans.

Supersomes™ Assay. Various human cytochrome P450-specific Supersomes™, such as CYP2D6 SUPERSOMES, are purchased from Gentest (Woburn, Mass., USA). A 1.0 mL reaction mixture containing 25 pmole of Supersomes™, 2.0 mM NADPH, 3.0 mM MgCl, and 1 μM of a compound of formula 1 is incubated at 37°C in triplicate. Positive controls contain 1 μM of Compound 1 instead of a compound of formula 1. Negative controls used Control Insect Cell Cytosol (insect cell microsomes that lacked any human metabolic enzyme) purchased from GenTest (Woburn, Mass., USA). Aliquots (50 μL) are removed from each sample and placed in wells of a multi-well plate at various time points (e.g., 0, 2, 5, 7, 12, 20, and 30 minutes) and to each aliquot is added 50 μL of ice cold acetonitrile with 3 μM haloperidol as an internal standard to stop the reaction.

Plates containing the removed aliquots are placed in ~20°C C. freezer for 15 minutes to cool. After cooling, 100 μL of deionized water is added to all wells in the plate. Plates are then spun in the centrifuge for 10 minutes at 3000 rpm. A portion of the supernatant (100 μL) is then removed, placed in a new plate and analyzed using Mass Spectrometry.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.
6. The compound of claim 1, selected from:

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<th>R²</th>
<th>R³</th>
<th>R⁴</th>
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<tr>
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<td>CD₂</td>
<td>CD₃CH₂CH₂</td>
<td>=O</td>
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<tr>
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<td>CH₁</td>
<td>CD₂CH₂CD₂</td>
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<tr>
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<td>CD₃CH₂CD₂</td>
<td>=O</td>
</tr>
<tr>
<td>141</td>
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<td>CH₃</td>
<td>CD₃CD₂CD₂</td>
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<tr>
<td>143</td>
<td>CD₃</td>
<td>CH₃</td>
<td>CH₃CH₂CH₂</td>
<td>F</td>
</tr>
</tbody>
</table>

7. The compound of claim 1, wherein each atom not specified as deuterium is present at its natural isotopic abundance.

8. A pyrogen-free composition comprising an effective amount of the compound of claim 1 and an acceptable carrier.

9. The composition of claim 8, wherein said composition is formulated for pharmaceutical administration and the carrier is a pharmaceutically acceptable carrier.

* * * * *